

Progestins and Antiprogestins in Clinical Practice

edited by

Régine Sitruk-Ware

*Hôpital Saint-Antoine
Paris, France*

Daniel R. Mishell, Jr.

*University of Southern California School of Medicine
Los Angeles, California*

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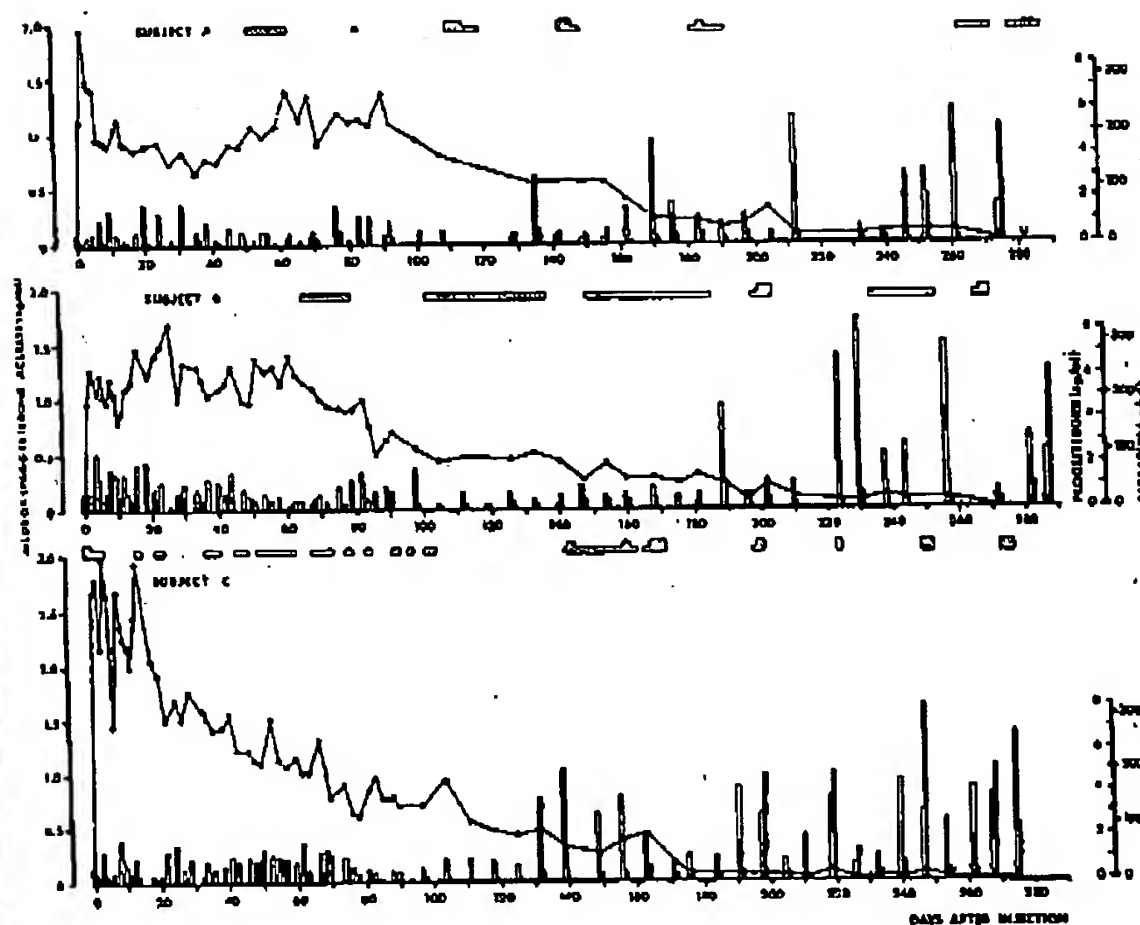


Figure 6 Serum medroxyprogesterone acetate (MPA, dots), estradiol (open bars), and progesterone (solid bars) concentrations in three women (subjects A, B, and C) following intramuscular injection of 150 mg depo-MPA. Hatched horizontal bars of full and half thickness indicate uterine bleeding and spotting, respectively. Undetectable levels of MPA are indicated by v. (From Ref. 11.)

V. ESTRANES: THE FIRST-GENERATION PROGESTINS

A. Structure and Function

The estrane progestins are derivatives of the testosterone molecule. Possibly, the most important estrane is 17α -ethinyl-19-nortestosterone, known under the generic names of norethindrone and, mostly in Europe, as norethisterone; it is abbreviated as NET. Figure 7 shows NET and its four derivatives which have been used in various combined oral contraceptives. These derivatives differ from the parent molecule by minor structural modifications, and they have to be

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Henzl and Edwards

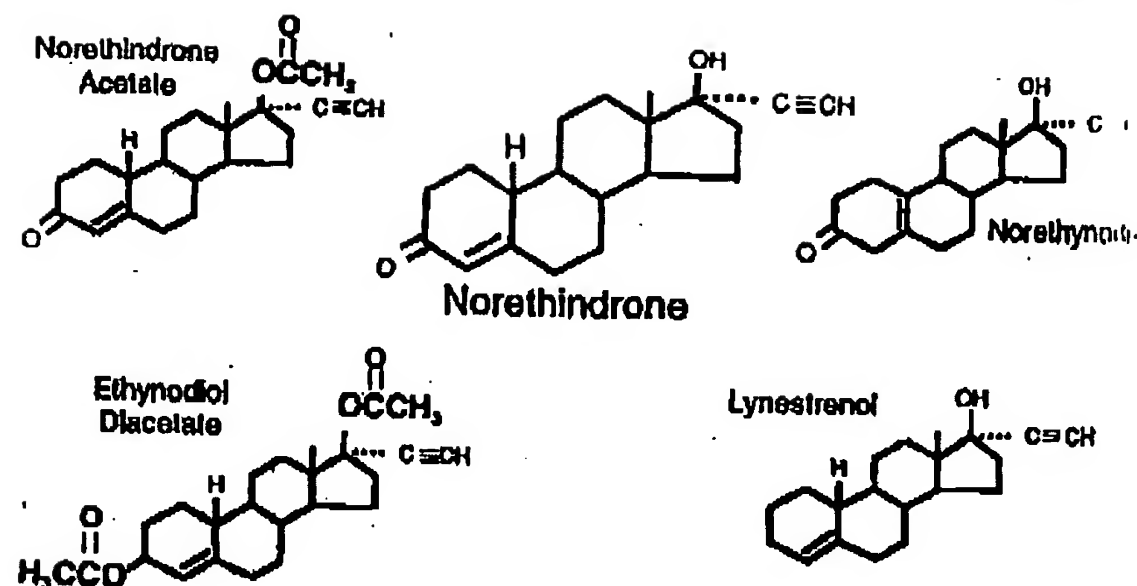


Figure 7 Norethindrone (NET) and its four derivatives. To become biologically active, these derivatives have to be metabolically converted to NET. (From Ref. 12).

metabolically converted to NET before they become biologically active (12). In this sense, they can be considered as prodrugs. Norethynodrel differs from NET by the position of the double bond in the A ring: in norethynodrel the double bond is between C-5 and C-10, whereas in NET it is between C-4 and C-5. This modification affords norethynodrel some degree of estrogenicity. Norethynodrel was the progestin component of the first combined OC; however, today it is rarely used. Lynestrenol is characterized by the absence of an oxygen function at the C-3. NET-acetate bears an acetoxy group at C-17. Ethinodiol diacetate bears acetoxy groups on both C-3 and C-17.

The development of norsteroids is an example of biochemical ingenuity and innovation (Fig. 8). Henzl (13) and Edwards and Henzl (14) have given a detailed account of the development of contraceptive steroids.

The cornerstone in the quest for highly potent orally active progestins was the recognition that removal of C-19 methyl radical profoundly changes the biological properties of both the progesterone and testosterone molecules. For progesterone, removal of C-19 methyl group resulted in 19-norprogesterone, the first compound found to be more potent than progesterone itself. However, this compound was only parenterally active. Removal of the C-19 methyl radical from testosterone resulted in the loss of androgenicity of the parent molecule. Earlier, it had been found that attachment of the ethynyl group in the α -position ($\cdots\text{C}\equiv\text{CH}$) at C-17 afforded the molecule oral activity. Combination

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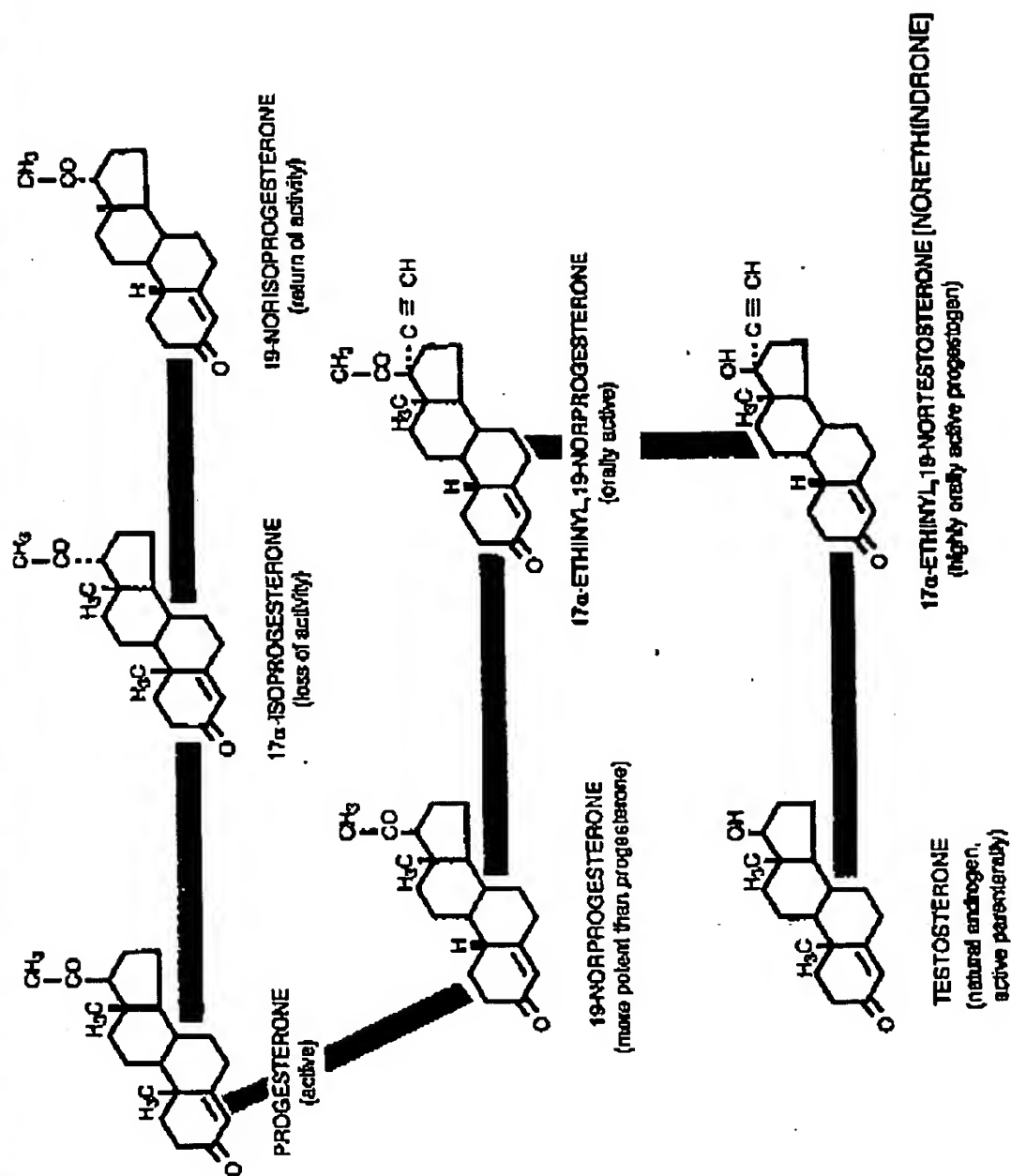


Figure 8 Development of norethindrone (for details see text). (From Ref. 6.)

of both described modifications (i.e., removal of the C-19 group and attachment of ethinyl group to C-17) resulted in norethindrone. This compound exhibited high progestational potency when administered orally and was the first oral progestogen more potent than progesterone given parenterally. The discovery of NET, accomplished by Djerassi et al. in 1951 (see details in Refs. 13 and 14), enabled the development of modern oral contraceptives. The synthetic process leading to NET, coupled with the earlier discovery that intermediate products for steroid synthesis could be obtained from roots of certain plants, principally of the genus *Dioscorea*, enabled the large-scale production of OC that made their wide distribution financially feasible.

Because NET is derived from testosterone, and "testosterone" is part of the chemical name of the compound, it is sometimes assumed that NET has androgenic properties. In fact, in the doses and combinations used in current clinical practice, NET does not exhibit any discernible clinical androgenicity. Interestingly, NET containing OC has been used in combination with a GnRH agonist for the management of hirsutism in women (15).

B. Pharmacokinetics and Metabolism

The four derivatives of NET have to be metabolically converted to NET to exercise their biological action. This conversion happens rapidly, with only NET being detected in the circulation within 30 min after oral administration of any of the derivatives (12). Compared with an intravenous dose, the bioavailability of NET given orally averages 60–70%, indicating a first-pass effect (12).

The single-dose pharmacokinetics of NET fits the two-compartmental model, with the $t_{1/2\alpha}$ of the rapid phase averaging 0.6 h and the slower $t_{1/2\beta}$ phase averaging 8.4 h (16). The pharmacokinetic parameters of NET are summarized in Table 1.

Table 1 Pharmacokinetic Parameters of Norethindrone (NET) in 20 Normal Adult Women After a Single Oral Dose of NET (1 mg) plus Ethinyl Estradiol (0.12 mg)

Parameter	Mean value \pm standard deviation
Maximum plasma concentration ($C_{p_{max}}$)	15.7 \pm 6.19 ng/mL
Time to maximum plasma concentration (t_{max}) of NET	1.17 \pm 0.65 h
Total area under plasma concentration vs. time curve (AUC)	84.5 \pm 27.6 ng \times h
Plasma half-life ($t_{1/2}$)	8.05 \pm 1.92 h

Source: Ref. 16.

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About 36% of the circulating NET is bound to serum hormone-binding globulin (SHBG), about 60% is bound to albumin, and the remainder circulates as free NET.

NET is mainly metabolized to glucuronide, but about 10-25% is metabolized to sulfate (12). The major plasma metabolite is the product of reduction of the A ring; namely, the 3 β -hydroxy-5 α -tetrahydro-derivative. This metabolite exhibits high affinity for the estrogen receptors, whereas NET by itself and other metabolites of NET do not (17,18). The estrogenic effects of NET have been demonstrated earlier; however, the explanation of the estrogenic activity of NET has been controversial (3). Besides the possibilities outlined in the foregoing, metabolic conversion of NET to EE has also been suggested as a reason for the estrogenic effect of NET. In perimenopausal women, the transfer constant in blood for the conversion of NET to EE was established at about 2%. Although small, this amount was considered sufficient to produce an estrogenic response (19).

VI. GONANE PROGESTINS OF THE SECOND GENERATION

A. Structure and Function

The gonane progestins are divided into two classes called the second and third generations. Compounds of the second generation include *dl*-norgestrel (NG) and levonorgestrel (LNG) (Fig. 9).

A brief discussion of the terms *optical isomerism* and *absolute configuration* is required to understand the differences in the stereochemical and biological properties of NG and LNG. Optical isomers are distinguished by their ability to rotate a plane of polarized light (sodium source) in solution. Thus, an isomer

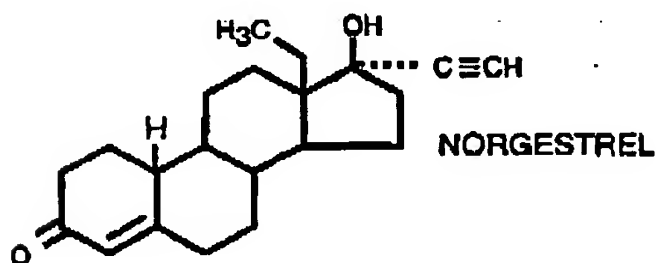


Figure 9 Levonorgestrel (LNG) is the *l* (–) enantiomer. Norgestrel (NG) is a racemic *d/l* (+/–) mixture composed of the depicted structure and its mirror image. Only the levorotatory enantiomer is biologically active.

that rotates the plane of polarized light in a clockwise direction is referred to as the dextrarotatory (*d*) or (+) enantiomer. Similarly, an optical isomer that rotates the plane of polarized light in the opposite direction is referred to as the levorotatory (*l*) or (−) enantiomer. An equal mixture of optical isomers is identified by the expression (+/−) and is often referred to as a *d/l* mixture (20).

Steroids prepared by total synthesis consist of a 1:1 mixture of *d* and *l* enantiomers. Norgestrel was the first progestin to be prepared by total synthesis and marketed as a *d/l* mixture. There are several disadvantages associated with the marketing of pharmaceutical products as *d/l* mixtures, such as the cost of synthesis and formulation. These disadvantages stem from the fact that the biological activity of a *d/l* mixture actually resides in only one of the optical isomers. In the case of NG, this prompted the development of synthetic methods that produced only the biologically active *levo* (−) enantiomer. As expected, the latter enantiomer, named levonorgestrel (LNG) exhibited twice the potency of NG in comparative bioassays. Thus, LNG was rapidly developed and soon replaced all NG-containing OC preparations.

The term absolute configuration refers to the actual arrangement of a molecule in space (21). There are various procedures available for determining the absolute configuration of a molecule, including X-ray crystallography, optical rotatory dispersion, and several chemical methods. Application of these procedures to several of the natural steroids revealed that progesterone has the absolute configuration represented by the structure depicted in Fig. 3 and not its mirror image. In fact, all steroids from plant and mammalian sources, and compounds derived from them, have the same absolute configuration (21–23).

Optical rotatory dispersion studies (24) and, subsequently, an X-ray crystallographic analysis (25) of LNG indicated that the biologically active enantiomer has the structure depicted in Fig. 9. This LNG has the same absolute configuration as the natural steroids, such as progesterone as well as clinically useful progestins described in this chapter. The name *D*-norgestrel has been employed to describe this circumstance. The use of the letters *D* and *L* originated from an early convention that was created to permit the unambiguous assignment of the absolute configuration to molecules bearing a single asymmetric carbon atom, such as glyceraldehyde and lactic acid (21). In an investigation of the structure of cholesterol, it was demonstrated that the hydroxyl-bearing carbon C-3 has the same absolute configuration as glyceraldehyde. Therefore, according to the convention, cholesterol would be categorized as *D*-cholesterol. Because the structure of LNG was correlated with that of cholesterol by X-ray studies, this enantiomer was called *D*-norgestrel (25). There is no relation between the sign of the optical rotation of an asymmetric substance [*d* or (+); *l* or (−)] and its absolute configuration, designated either *D* or *L* (see foregoing for details).

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In recent years, the International Union of Pure and Applied Chemistry has adopted a more rigorous convention to define the absolute configuration of asymmetric molecules (26). However, the old convention is still used for the amino acids and sometimes for LNG.

The successful synthesis of LNG enabled the development of an OC with an extremely low progestin content. In one monophasic combination pill, 150 μ g LNG is used with 30 μ g EE. In the triphasic 21-day combination, a dose as low as 50 μ g is given for the first 5 days, followed by 75 μ g daily for 6 days, and 150 μ g daily for the last 12 days. The progestin-only method employs a daily dose of 30 μ g in a continuous, uninterrupted treatment regimen. For emergency contraception (interception), 750 μ g LNG are recommended. In describing the pharmacokinetics of LNG, we will concentrate on these three doses.

B. Pharmacokinetics and Metabolism

The pharmacokinetics of the two optical isomers of *dl*-norgestrel differs substantially. Notably, the half-life of both the α - and the β -phase of the inactive dextrarotatory enantiomer is longer than that of LNG. Thus, in evaluating the pharmacokinetic data of NG, we need to consider whether LNG or the racemic mixture was assayed.

Fotherby has most comprehensively reviewed the pharmacokinetics of LNG, and his survey is the main source for the following description of the pharmacokinetics of LNG (27,28).

The pharmacokinetics of LNG displays certain unique features (Table 2). The compound's $t_{1/2}$ is about 14 h, with a range of 8–25 h. Only progestins of the third generation have similarly long $t_{1/2}$. Most importantly, the time required for the circulating levels of LNG to decline by 50% is about 15 h, whereas for NET, it is about 7 h. The difference in the elimination time is one of the reasons why contraceptive doses of NET must be higher than those of LNG. Concentrations of circulating LNG also vary widely within subjects and between individual subjects. That concomitant administration of estrogens is associated with a marked increase of the circulating concentrations of LNG is one of its important characteristics (28) (Fig. 10).

Another interesting feature of NG and LNG is their relation to SHBG. LNG, at a dose of 150 μ g/day without an estrogen, decreases plasma concentrations of SHBG by 50%. However, SHBG is strongly affected by the estrogen component of the combined OC. EE given alone will increase plasma SHBG two- to threefold from baseline. However, it is important to realize that NG and LNG are effective antiestrogenic agents, which suppress estrogen-induced formation of SHBG. Monophasic combination treatment with 300 μ g NG and 30 μ g EE has been associated with only a minor (26%) and not statistically significant SHBG elevation from baseline (29). Results in users of triphasic LNG

Table 2 Pharmacokinetic Parameters of Levonorgestrel (LNG) given orally in Three Contraceptive Regimens: (a) Low-Dose Continuous Contraception (30 μ g/day); (b) Monophasic Combination of 150 μ g LNG with 30 μ g Ethinyl Estradiol (EE) per day; (c) Emergency Contraception (750 μ g)

Parameter	Plasma concentration of LNG (ng/ml) after oral dose of		
	30 μ g	150 μ g + 30 μ g EE	750 μ g
	2 studies <i>n</i> = 8	6 studies <i>n</i> = 54	3 studies <i>n</i> = 26
Time to maximum plasma concentration (<i>t</i> _{max} ; h)	N/D		
Range of means across studies		1.0–2.4 ^b	1.9 ^c
Range of means of individual patients		0.2–3.1 ^b	1.0–2.7 ^c
Mean after achieving steady state		1.0 \pm 0.2	
Maximum plasma concentration (<i>C</i> _{max} ; ng/mL)	N/D		
Range of means across studies		3.2–3.8	9.0–11.2
Range of means of individual patients		1.5–6.8	8.1–18.4
Mean after achieving steady state		6.8 \pm 2.1	7.1 \pm 2.8
Total area under plasma concentration vs. time curve (AUC; ng \times h)			
Range of means across studies	6.7 ^a	20.2–37.8	116.0–124.0 ^d
Range of means of individual patients	3.5–11.1	14.0–120.0	41.0–177.0 ^d
Mean after achieving steady state		115.0 \pm 52.0	118.0 \pm 50.0
Terminal plasma elimination half-life (<i>T</i> _{1/2β} ; hs)			
Range of means across studies	13.7–14.8	8.0–25.0	8.9–14.5
Range of means of individual patients	7.4–23.0	8.0–35.0	1.9–18.5
Mean (\pm SD) after achieving steady state		23.5 \pm 8.6	12.0 \pm 4.8

^aData of three women.

^bData of 42 women.

^cData of 10 women.

^dData of 16 women.

Legend: *n*, total number of women in studies; N/D, not determined.

Source: Ref. 27.

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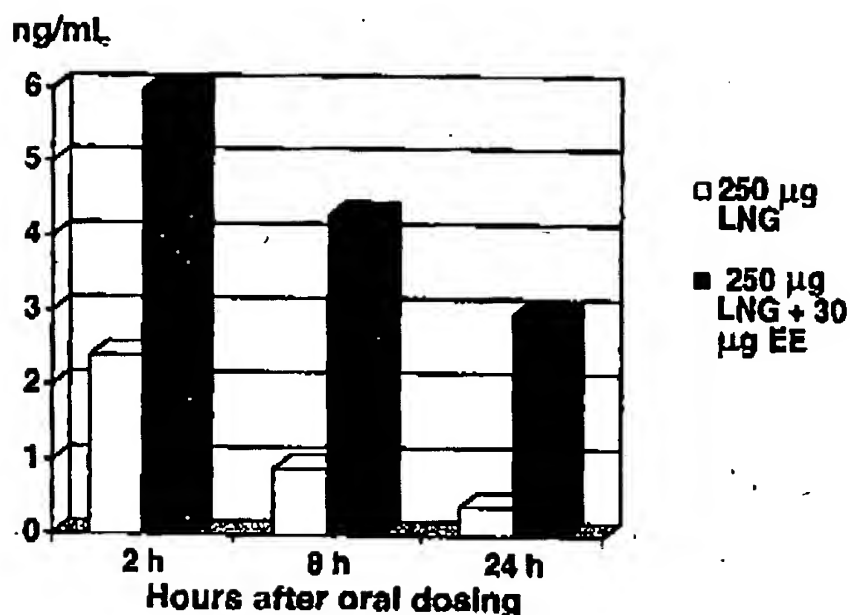


Figure 10 Mean serum levonorgestrel (LNG) concentrations in women receiving LNG alone (open columns) or with ethinyl estradiol (EE) (hatched columns). Concomitantly administered EE substantially elevates blood concentrations of LNG. (From Ref. 28.)

combination are inconsistent. After six treatment cycles, some studies reported elevations up to 70% from baseline (30-32), whereas at least one investigator detected a 6% decrease in SHBG, also after 6 months of treatment (33). The changes in SHBG concentrations should be viewed in the context that the use of combination oral contraception with cyproterone acetate and EE is associated with a fivefold increase of SHBG (see also Fig. 12).

LNG binds more strongly to SHBG than other progestins. This interaction does not explain the wide variability of blood levels of LNG after oral dosing or that circulating concentrations of LNG are elevated in the presence of estrogens.

Table 2 gives the elemental pharmacokinetic parameters for LNG. Few data are available for the 30-µg dose because only a total of eight women were examined in two studies. The $t_{1/2\beta}$ ranged in individual women from 7 to 23 h, with an average from 13 to 15 h.

More data are available for the contraceptive combination of 150 µg LNG + 30 µg EE. In six studies, 54 women were studied. There was a wide variability of values between individual subjects and among individual studies. Maximum serum levels ranged from 1.5 to 6.8 µg/L and were attained within 1-2 h after oral dosing. The mean $t_{1/2}$ ranged from 8 to 25 h. Maximum serum LNG levels after the single "interceptive" dose of 750 µg were three to four times higher, and the area under the concentration-time curve (AUC) was three to five times

greater than after ingestion of the combined dose of 150 μ g with 30 μ g of EE. These high LNG levels were necessary for an effective emergency contraception.

Pharmacokinetics of progestins released from silastic implants, vaginal rings, and intrauterine devices are discussed in other chapters of this book.

LNG is metabolized by reduction of the A ring, and conjugation to glucuronic and sulfuric acid, and further by oxidation at C-2 and C-16. About 20-67% of the administered radioactive dose is excreted in urine, and 21-34% is excreted in the feces. No metabolite with estrogenic activity has been identified (12).

VII. NORPREGNANES AND OTHER MODIFIED PROGESTINS

A. 19-Norpregnanes

The 19-norpregnanes are a cross between the pregnanes and estranes. These compounds are derived from progesterone, but lack the C-19 methyl radical (Fig. 11). Norgestrol, an important member of this series, is currently undergoing extensive clinical investigation as a contraceptive implant. It has been intensively studied for its ability to inhibit uterine contractions (34,35).

Nestorone (NES) is another 19-norpregnane of the 17 α -acetoxy-progesterone series, which bears a methylene group on C-16. Thus, the compound is 16-methylene-17 α -acetoxy-19-norpregn-4-ene-3,20-dione. In receptor assays NES showed progestational effects equal to or better than LNG, without estrogenic, androgenic, or anabolic activities (36). However, NES binds to glucocorticoid receptors. NES has low oral, but high parenteral progestational activity. Therefore, The Population Council is studying NES as a contraceptive in subdermal implants, vaginal rings, and transdermal formulations. The compound is suitable for nursing mothers because of its low oral action (see also Chap. 7).

B. Other Modified Progestins

Dienogest is an interesting estrane. In this compound, the cyanomethyl group ($\cdots\text{CH}_2\text{CN}$) has replaced the C-17 ethinyl group ($\cdots\text{C}\equiv\text{CH}$). There is an extra double bond between C-10 and C-11. Dienogest is 100% orally available. The terminal half-life of dienogest varies from 8 to 10 h, which is slightly longer than $t_{1/2}$ of NET, but it is shorter than that of LNG. It is claimed that the compound is without any androgenic activity and, supposedly, it affects glucocorticoids to a lesser degree than mifepristone (RU 486). The compound suppresses endometrial growth and was tested in the management of endometriosis. Preliminary studies in women with mild endometriosis have shown some beneficial effects. The

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